IMPROVED SYNTHETON SYNTHESIS

Background of the Invention:

(1) Field of the Invention

The present invention relates to a novel one-pot synthesis of the commercially important syntheton lower alkyl 4-cyano-3-hydroxybutyrate (ACHB) via the unisolated intermediate alkyl 4-halo-3-hydroxybutyrate which preferably can be either the 4-iodo (AIHB) or 4-bromo (ABHB) compound. In preferred embodiments, the ethyl esters EIHB or EBHB are utilized. The synthesis is applicable to optically active or racemic product. It provides the desired end product in high yield, at high purity and is readily scaleable to commercial size runs employing reagents that do not pose environmental issues and minimize undesirable side reactions.

(2) Description of Related Art

The ethyl esters ECHB and the intermediates EIHB and EBHB are known compounds, which have been made by a number of previously reported syntheses. Thus, for example, in US Patent No. 6,114,566 to Hollingsworth *et al.*, (R)-ECHB (compound 4) is produced in three steps starting from (S)–3-hydroxy-γ-butyrolactone (3) via (S)-EBHB (5) and the corresponding unisolated optically active 3,4-epoxide (6). In the first step, the lactone (3) was reacted with 30% hydrogen bromide in acetic acid at 60° C. for 4 hours. Ethanol was added and the reaction mixture was allowed to sit at constant temperature for 4-6 hours. The mixture was concentrated, then taken up in toluene and after being neutralized, concentrated to provide (S)-EBHB in 90% crude yield. After distillation, the yellow oil product tested at greater than 95% purity.

The (S)-EBHB intermediate (5) was treated with NaCN in aqueous ethanol at 50°C. Workup by rotary evaporation of solvent and extraction in ethyl acetate provided (R)-ECHB (4) in 95% crude yield as a yellow oil which was purified further by distillation. While the crude yield is high in this method, deficiencies as to its applicability to commercial scale remain. Thus, the availability of the 30% HBr solution in acetic acid is limited in industrial scale and work up is complicated because of the usage of acetic acid. Our results duplicating the conditions used by Hollingsworth et al.,

showed that the unwanted side product ethyl 4-hydroxycrotonate is formed in 3 to 10% yield. Hydrolysis of the esteric product to the corresponding acid during the cyanization step is another problem that we observed. Moreover, we observed that when the lower yields of ethyl 4-hydroxycrotonate are found, there was a corresponding increase in the amount of hydrolysis.

There is further literature describing use of TMSCl/NaI/CH_2Cl_2 as a ring opening reagent, Tetrahedron Letters, 28(16), 1781-1782(1987) (Larcheveque, M. and Henrot, S.), Tetrahedron, 46(12), 4277-4282(1990) (Larcheveque, M. and Henrot, S.) and WO9306826. As Larcheveque and Henrot reported, the ring opening of the (S)-3-hydroxybutyrolactone was pursued under different conditions to get the iodohydrin product, (S)-ethyl 3-hydroxy-4-iodobutyrate. Taking advantage of the versatility of trimethylsilyl iodide, they succeeded in obtaining the iodohydrin in moderate yields. However, several problems in utilizing this method were anticipated on large scale preparation. TMSI is rather expensive and very reactive which causes difficulties in handling. As published by others such as G. Olah (Tetrahedron, 1982, 38, 2225-2227), these types of reactions usually cause various side reactions, complicating the purification processes.

Summary of the Invention

The present invention relates to an improved synthesis of the commercially important syntheton ACHB starting from the readily available 3-hydroxy-γ-butyrolactone. The reaction employs a single pot procedure without isolation or purification of the intermediates. It has the advantage over procedures previously employed in the art of using reagents and conditions which minimize undesired side reactions and which can be readily employed at commercial scale. The product is produced in high yield and is readily purified to provide an excellent intermediate for further synthesis of commercially important products such as L-carnitine and the pharmaceutically important active substances used in HMG-coA reductase inhibitor products such as Lipitor® (Atorvastatin, Pfizer).

In the first step of the instant process, the starting 3-hydroxy-γ-butyrolactone, either in racemic or optically active form, is subjected to ring opening using a haliding

agent. This reaction proceeds faster, cleaner and in quantitative yield when conducted in the presence of an acylating agent and a lower alkanol. Suitable haliding agents include reagents which provide either bromide or iodide which reagents include, for example, hydrogen bromide in solution or gaseous form, hydrogen iodide, trimethylsilyl bromide or iodide, or an alkali metal bromide or iodide such as, preferably, sodium bromide in the presence of a mineral acid such as hydrochloric acid, sulfuric acid and the like. Suitable acylating agents include lower alkanoyl halides such as acetyl chloride or acetyl bromide, alkanoic anhydrides, such as acetic anhydride, lower alkyl alkanoates such as ethyl esters of lower aliphatic carboxylic acids, most preferably ethyl acetate or ethyl formate, and mixtures thereof. As used in this specification, the term "lower' includes moieties having 1-4 carbon atoms. An alternative reagent useful in the practice of this invention comprises a lower alkanoyl bromide which serves both functionalities. A preferred lower alkanoyl bromide is acetyl bromide. It is highly desirable to avoid the use of hydrogen bromide in the presence of acetic acid in this reaction to avoid undesirable side reactions.

The first step can be carried out at any convenient reaction conditions as such conditions are not narrowly critical. A suitable reaction temperature can be within the range of 0° to 100°C. A preferred temperature is within the range of 50-60°C. After ring opening, the carboxylic acid produced is esterified in the presence of an alkylating agent such as a lower alkanol, most preferably ethanol, to provide the desired intermediate product AIHB or ABHB. Both the acylating agent and the lower alkyl may be present in greater than equimolar amounts to the other reactants to thereby serve as solvent for the reaction.

It should be noted that the first step reaction has not been carried out successfully with chlorinating agents such as hydrogen chloride, sodium chloride/hydrogen chloride or trimethylsilyl chloride.

The desired ring opening reaction is achieved in accordance with the procedures of the present invention so as to produce either AIHB or ABHB in quantitative crude yield and in a purity which allows this intermediate to be used directly in the next step without need for isolation and purification.

In the second step of the present process, the crude, unisolated AIHB or ABHB product obtained in the first step is reacted with a source of cyanide ion to yield the desired product ACHB, most preferably as the ethyl ester (ECHB). A suitable source of cyanide ion for this reaction step is an alkali metal cyanide, most preferably sodium or potassium cyanide. The cyanation reaction is conveniently carried out using the same solvent used in the first step, that is a lower alkanol such as ethanol, which may be present in aqueous mixture (ratio 1:10 to 10:1 ethanol to water). As in the first step of the process, the temperature conditions employed are not narrowly critical. However, due to the exothermic reaction produced by the addition of the cyanide reagent to the AIHB or ABHB intermediate, it is desirable to initiate the reaction at a temperature of about 25°C and to maintain a temperature at about that level or lower by cooling. After completion of the addition of the cyanide ion reagent, the reaction mixture can be heated to a temperature of about 35°C for a period of from 1 to 24 hours, most preferably for about 6 hours.

It is important to assure that the pH of the reaction mixture is within a range of from 7 to 11, preferably 7.5-10.5, most preferably from 8-9.5. If necessary, a hydrogen halide, such as hydrogen iodide or hydrogen bromide, may be added to effectuate the pH adjustment. It has been unexpectedly discovered that by conducting the reaction in this manner, side reactions known to occur when the reaction with cyanide ion is carried out under strongly basic conditions with EBHB in water or water/alcohol mixtures (ethyl 4-hydroxycrotonate formation and hydrolysis of an ester) are substantially reduced or even eliminated altogether. In contrast to the 3~10% of the side product ethyl 4-hydroxycrotonate observed when prior art aqueous conditions are employed, a total of <2% of ethyl 4-hydroxycrotonate by GC peak is usually observed when the present conditions are used. Moreover no detectable level of the hydrolysis product is seen.

The reaction mixture can then be worked up in a conventional manner by extraction with a suitable organic solvent or solvent mixture and concentration of the reaction solvent. The final product can be purified in a batch or continuous mode by vacuum fraction distillation to provide the desired CHB in high yield and purity suitable for use in commercial scale, pharmaceutical preparations of medicinally important final products.

The practice of the present invention is further illustrated by the following non-limiting examples.

Example 1

(A) With Hydrogen Bromide/Acetyl Chloride/Ethyl Acetate/Ethanol As Ring Opening Reagent

A mixture of 10g of (S)–3-hydroxy-γ-butyrolactone and 50 ml of ethyl acetate was cooled to 0°C. With stirring, 7.7 g of acetyl chloride was added slowly. A total of 50 ml of 6N HBr in ethanol (50 ml EtOH and 24g (3eq HBr) was then added and the mixture was warmed up to 50 °C and maintained at that temperature for 3 hours. The mixture was concentrated to remove most of the ethyl acetate. Ethanol, 50 ml, was added to the residue and the resulting solution was stirred at 50°C for 5 hours . The mixture was concentrated to remove most of the solvents. The resulting product normally was obtained as a slightly yellowish oil in quantitative yield. However, it is used in the next step directly without further isolation or purification.

(B) With Hydrogen Bromide/Ethyl Acetate/Ethanol As Ring Opening Reagent

To a mixture of 10g of (S)–3-hydroxy-γ-butyrolactone and 50 ml of ethyl acetate, 50 ml of 6N HBr in ethanol (50 ml EtOH and 24g (3eq) HBr) was added. The mixture was warmed up to 50°C and maintained at that temperature for 5 hours. The mixture was concentrated to remove most of the ethyl acetate. Ethanol, 50 ml, was added to the residue and the resulting solution was stirred at 50°C for 5 hours. The mixture was concentrated to remove most of the solvents. The resulting product normally was obtained as a slightly yellowish oil in quantitative yield, however it can be used in the next step directly without further isolation or purification.

(C) With Acetic Anhydride/Ethyl Acetate/Ethanol/Hydrogen Bromide As Ring Opening Reagent

To a mixture of 10g of (S)–3-hydroxy-γ-butyrolactone, 9.2 ml of acetic anhydride and 50 ml of ethyl acetate, 50 ml 6N HBr in ethanol (50 ml of EtOH and 24g (3eq) HBr) was added and the mixture was warmed up to 50°C and maintained at that temperature for 3 hours. The mixture was concentrated to remove most of the ethyl acetate. Ethanol, 50 ml, was added to the residue and the resulting solution was stirred at 50°C for 5 hours.

The mixture was concentrated to remove most of the solvents. The resulting product normally was obtained as a slightly yellowish oil in quantitative yield, however it can be used directly in the next step without further isolation or purification.

(D) With Acetyl Chloride/Ethyl Acetate/Ethanol/Sodium Bromide As Ring Opening Reagent

A mixture of 10g of (S)–3-hydroxy-γ-butyrolactone and 50 ml of ethyl acetate was cooled to 0°C. With stirring, 7.7 g of acetyl chloride was added slowly. 50 ml of 6N HBr in ethanol (50 ml EtOH and 24g (3eq) HBr) was added and the mixture was warmed up to 50°C and maintained at that temperature for 3 hours. The mixture was concentrated to remove most of the ethyl acetate. Ethanol, 50 ml, was added to the residue and the resulting solution was stirred at 50°C for 48 hours. The mixture was concentrated to remove most of the solvents. The product normally was obtained as a slightly yellowish oil in quantitative yield, however it can be used directly without further isolation or purification.

(E) With Acetyl Bromide/Ethanol As Ring Opening Reagent

A mixture of 100g of (S)–3-hydroxy-γ-butyrolactone , 136g of ethanol, and 400 ml of ethyl acetate was cooled to 0°C. With stirring, 241 g of acetyl bromide was added slowly. The mixture was warmed to 50°C and maintained at that temperature for 5 hours. The mixture was concentrated to remove most of the ethyl acetate solvent. Ethanol, 400 ml, was added to the residue and the resulting solution was stirred at 50°C for 5 hours. The solution normally was slightly yellowish and could be concentrated or used directly in the next step, as shown in Example 2, without isolation or further purification. The yield was about quantitative.

Example 2

(A)One-Pot Procedure for Ethyl 4-Cyano-3-Hydroxybutyrate (ECHB) Preparation

To the solution obtained from Example 1 (starting from 20g of (S)-3-hydroxyGBL) , was added a solution of NaCN (additional mineral acid such as HBr or HCl may be added to adjust pH to 8 ~9.5 if necessary).

The solution from above was cooled to 25°C. A solution of 22.6g of NaCN in 40 ml of water was added over a period of 20 minutes. The reaction temperature was kept under 25°C during the addition. After addition, the reaction mixture was stirred at 25°C for 1 hour. The reaction was warmed to 35°C for 6 hours. The solution was cooled to 25°C and extracted with 100 ml of methylene chloride twice. After concentration, 33g of crude ethyl 4-cyano-3-hydroxybutyrate was obtained. Analyzed yield by quantitative GC averaged >80% yield of product.

The ECHB product, in R configuration, was further purified in a batch or continuous mode by vacuum fraction distillation. Recovery for distillation is > 95%.
b.p. 270 °C (116°C/0.8mmHg)
^{1}H-NMR (CDCl3, 250 MHz), δ ppm: 4.36(m, 1H.); 4.21(q, J=7.0, 2H); 3.49(s, 1H); 2.64(m, 4H); and 1.30(t, J=7.0, 1H). [Lit. (US Patent No. 5,155,251) (^{1}H-NMR($CDCl_3$, 200 MHz), δ ppm: 4.36(m, 1H.); 4.18(q, 2H); 3.84(s, 1H); 2.64(m, 4H); and 1.29(t, 1H)].
^{13}C-NMR ($CDCl_3$, 250 MHz), δ ppm: 171.96, 117.34, 64.54, 61.68, 40.40, 25.44, and 14.49. [Lit. (US Patent No. 6,114,566A) ^{13}C-NMR ($CDCl_3$, 75 MHz), δ ppm: 171.3, 117.2, 63.8, 61.0, 40.1, 24.9, and 13.9].
$[\alpha]D^{25}$ = -32.7 °(C = 1, $CHCl_3$) (Lit. (US Patent No. 5,155,251) $[\alpha]D^{25}$ = -33.1 °(C = 1.08, CHCl3).
% e.e. > 98% (by GC, maintained optical purity of the lactone starting material).

All references cited herein are incorporated by reference. The present invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof and accordingly, reference should be made to the appended claims, rather than to the foregoing specification, as indication of the scope of the invention.